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Review

Genetic and immunological biomarkers in the diagnosis of pulmonary tuberculosis: A literature review for miRNA and cytokine characterization

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Abstract

There is a sensitive interaction in the relationship between the Mycobacterium tuberculosis that causes tuberculosis disease (TB) and its host. This interaction significantly affects the course of the infection. Unfortunately, scientific studies continue without slowing down this disease, which remains popular among the infectious diseases with the highest mortality rate. Although the importance of genetics and the immune system in the host-bacteria relationship is emphasized, immunopathological events still need to be fully elucidated.

The molecular events between Mycobacterium tuberculosis and the host dictate the course of infection. Different expression levels of miRNAs in this infection continue until the polarization of macrophages. In addition, studies have shown that miRNAs also affect cytokine release in this cellular immune process. This review aimed to reveal how M. tuberculosis affects the course of host miRNAs during active infection and how cytokine levels change due to this interaction by reviewing the recent literature. This study will discuss the implications of using miRNA profiles and cytokine levels as biomarkers for the onset, maintenance, and termination of active TB.

Keywords

Cytokine, Immunity, miRNA, Pro-Inflammation,Tuberculosis

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Introduction

According to data from the World Health Organization, TB still ranks in the top 10 leading causes of death centuries after its discovery. Its popularity is maintained because 10 million people were still diagnosed with Tuberculosis in 2019 (available at: https://www.who.int/teams/global-tuberculosis-programme/tb-reports). However, Turkey's 2020 Tuberculosis Control Report shows that the incidence has decreased to 14.1 per 100,000 (available at: https://hsgm.saglik.gov.tr/tr/tuberkuloz-istatistikler). This decline in incidence in Turkey and worldwide indicates that saving one life can prevent hundreds of thousands of people from becoming infected.

It is crucial to rapidly improve current diagnostics and treatments apart from the traditional ones through more technological and individualized approaches and to continue this fight against TB in a determined manner [1-3]. Despite the astonishing progress in diagnosing and treating TB since its inception and the decline in incidence, it seriously threatens public health.

M. tuberculosis is a bacillus-shaped bacterium that grows slowly in culture and can be stained with acid-alcoholic dyes thanks to the mycolic acid in its cell walls. Although this type of bacteria can infect many mammalian species, humans are the only reservoir, and, with some exceptions, the only transmission is from person to person [4].

M. tuberculosis can direct its relationship with its host through its many structural components. These structural components have formed a specific pathogenesis system for the bacterium. In fact, the extent of infection and the localization of the bacteria depend on the interactions between the bacteria and its host [5]. This pathogenesis manifests itself as an innate and acquired immune response.

Table 1. Regulatory roles of some miRNA in the host immune system against M. tuberculosis infection.

miRNA	Function	References
miR-142-3p	Phagosome maturation, autophagy, and apoptosis	[33, 36, 38]
miR-146a/b	Regulation of TLR and RLR pathways	[37, 38]
miR-155		
miR-21		
miR-20a	Immun response, autophagy, and apoptosis.	[26, 43]
Let-7f	Immun response	[26, 39, 43]
miR-23a-5p		
miR-223		
miR-125a-3p		
miR-29a		
miR-1224	Lipid metabolism and energy, macrophage metabolism	[14, 33, 44]
miR-484	Lipid metabolism and energy	[14, 33]
miR-17-5p	Lipid metabolism and energy, autophagy, and apoptosis	[14, 26, 43]
miR-27	Lipid metabolism and energy	[14, 26, 44]
miR-425		
miR-1293		
miR-96		
miR-33	Lipid metabolism and energy, macrophage metabolism	[14, 33, 44]
Let-7e	Autophagy and apoptosis	[14, 19, 33]
miR-20a-5p		
miR-145		

The innate immune response is the initial response following recognition of the tubercle bacillus by host macrophages. This event triggers the host gene expressions and release of cytokines. Acquired immune response is the control and enhancement of an existing immune response [8]. CD4 and T helper cells play a major role in the adaptive immune response [6,7].

Cytokines and subgroups of cytokines are effective molecules that increase inflammation and proinflammation events and recruit other subgroups for cellular immunity. Studies have shown that TB's cytokine levels are unevenly distributed [8,9]. This profile of cytokines can be used as diagnostic biomarkers and determination of the stage of the disease [8,10,11].

MicroRNAs (miRNAs) play a role in biological mechanisms, primarily through their control at the transcription level. The relationship of miRNAs, which came to the fore with cancer research and was later developed and studied in many diseases and agents in infectious diseases such as Tuberculosis, which has a high mortality rate, has been revealed [10,12,13,14].

miRNAs are generally 20-22 nucleotides long and are conserved across species [15]. Studies have shown that miRNAs have a role in immune system regulation against many pathogens, including M. tuberculosis [10,16]. miRNAs follow a similar pathway to macrophages in regulating the innate immune response. It also has significant roles in rearranging the host transcriptome to inhibit bacteria effectively [17].

Studies have also shown that M. tuberculosis predisposes to pathogenicity by restricting host-mediated antibacterial signalling pathways by using miRNAs. In contrast, the host response attempts to inhibit bacterial proliferation by increasing processes such as autophagy. The host provides this protection using miRNA [18].

Aim of the work

Despite advances in health technology, TB remains a threat today; it is evident that early diagnosis and treatment of this disease require quick steps to prevent contagion. Therefore, the purpose of this article is to present the successful results of early diagnosis and treatment in TB disease, based on the literature in addition to standard definitions and procedures, or even just recent developments, according to the cytokine and miRNA profiles in the host.

Tuberculosis immunology and cytokines

M. tuberculosis is an obligate intracellular bacterium. When bacteria enter the cell, they can escape from the immune system's fighters thanks to their virulence factors and use the host's defence system to their advantage. TB, a classic example of infection, can progress from latent to active disease according to the response of the host immune system [19].

Innate immune response and acquired immune response play a role in TB infection. The most critical step of the innate immune response is the early immune response. Bacteria, which overcome the host's physical barriers, such as mucosa, and reach the alveoli, encounter macrophages here. The Toll-Like Receptor (TLR) in macrophages recognizes the bacteria, creates a signal against it, and invites other immune system elements to the environment [20]. "Pathogen-associated molecular patterns" (PAMP) released by bacteria stimulate the dendritic cells (DC) of the host [20,21]. Mycolic acids in bacteria

can stimulate natural killer cells (NK). B and T cell-mediated systems have developed in the acquired immune response. Monoclonal antibodies released from B cells and CD4/CD8 released from T cells are primary molecules of the system [22,23]. IFN-γ, TNF-α, IL-6, and Interleukin1 beta (IL-1β) are major molecules in the early pro-inflammatory process. While IL-2 acts as an NK activator, IL-12 is the protective element of the immune system; IL-6 is involved in forming T and B-cell-mediated immune systems [23].

Cellular immunity together with cytokines are mediators of the inflammatory response in TB. It has been shown in studies that lymphocytes released from T cells stop infection by limiting bacterial growth [24]. In addition, activated oxygen radicals produced from macrophages are released into the environment with the help of cytokines released from T cells, especially IFN-γ and TNF-α [25]. Thanks to these radicals, bacterial death becomes inevitable. In addition, IL-13, IL-10, IL-5, and IL-4, which are T-helper two cytokines, affect the course of the disease (Figure 1) [24, 25].

Contrary to this system developed by the host, bacteria have developed a system according to themselves. M. tuberculosis has serious strategies to protect itself from the host's defence system. They stimulate the release of IL-10 by T cells, and IL-10 release works inversely proportional to IFN-γ release. In this way, they develop a protective mechanism [26].

Seyedhosseini et al. [27] have determined the plasma levels of IL-17, IL-6, and TGF-β in healthy control groups, newly diagnosed active tuberculosis, and TB patients being treated. As a result, IL-6 plasma level was found to be higher in patients newly diagnosed when compared with both healthy subjects ($P = 0.002$) and TB patients receiving treatment ($P<0.0001$) [27]. For that reason, new therapeutic approaches against Tuberculosis aim to neutralize IL 6-induced cellular activation by lowering the IL 6 level via monoclonal antibodies. In addition, Adanwah and colleagues showed that IL-6 levels could be used as a marker for tuberculosis classification due to specific differences in IL-6 levels between tuberculosis patients and asymptomatic contacts [28].

IL-17 and TGF-β were significantly overexpressed in patients with active tuberculosis (newly diagnosed) compared to those on TB treatment and healthy individuals [28]. In addition, a study has shown that active and latent TB patients express elevated levels of IL-17 in their lung tissue samples, which is not shown in blood samples [29].

Mirzaei et al. [30] investigated TNF-α serum levels between the healthy control group and TB patients. According to these findings, they reported that TNF-α concentration was considerably higher in TB patients compared to the healthy group ($P<0.05$) [30].

MicroRNAs and biogenesis

In the miRBase online database, 38589 precursor and 48860 mature miRNAs are listed and available to researchers (Version 22.2, September 2022). miRNA maturation proceeds in stages. First, Drosha (RNA polymerase III) and a hairpin-shaped pre-miRNA are formed with a cofactor (DGCR8) and pri-miRNA. The pre-miRNA is then transported GTP-bound from the nucleus to the cytoplasm, where it continues to be processed. The pre-miRNAs in the cytoplasm bind to the Dicer enzyme, and this enzyme cuts to form mature miRNAs. This cut initiates the formation of RISC (RNA-induced silencing complex). As a result, one strand of this double-stranded mature miRNA is broken down, and the other strand joins with RISC. This splicing directs the miRNA to bind to the 3' UTR region of the mRNA, and mRNA degradation occurs [31,32].

miRNAs and M. tuberculosis

miRNAs' functions are increasing daily thanks to new-generation sequencing and advanced molecular techniques. Scientific studies have demonstrated the roles of miRNAs in metabolic diseases, infectious diseases, and even neurodegenerative diseases, especially in cancer. miRNA expression levels in host body fluids have been used in the early diagnosis and determination of the course of the disease in infectious agents. It is a drug target in viral infectious diseases such as hepatitis C [31].

The immune system works perfectly against factors such as Mycobacterium tuberculosis, an intracellular pathogen. Likewise, these intracellular pathogens have developed excellent mechanisms to ignore the host immune system. A situation that can be called a war of powers has arisen. As a result of the research, it has been shown that the most potent strategy implemented in this war is the miRNA mechanism [33]. miRNAs play critical roles in activating cytokine signaling, triggering immune system cells, developing, and even proliferation. It has been reported that miRNA varieties, including miR-155, miR-21, and miR-146a play significant roles in this immune response mechanism (Figure 2) [34].

miRNA-Cytokine Characterization in Tuberculosis Disease

During a bacterial infection, bacterial recognition by macrophages and phagocytosis are the most basic steps. M. tuberculosis is aware that this step is dangerous. This awareness has taught it to block the level of actin that promotes phagosome maturation. They developed this mechanism in the form of inhibition of proteins involved in the formation of actin. They achieve this inhibition by increasing miR-142-3p [35].

Cavusoglu C. et al. [36] investigated miRNA and cytokine characterization in TB disease by grouping them into active and latent Tuberculosis. They have contributed extensively to the literature by including M. tuberculosis genotyping, pre-treatment, and post-treatment follow-ups in their study group. Their study showed a statistically significant decrease in the expression of miR-449a, miR-38, miR-590-5p, miR-15a-5p, and miR-454-3p in the comparison of miRNA expressions between the patient group and the healthy control group before treatment. Compared to healthy controls, the cytokine expressions of the patient group before treatment decreased significantly. In contrast, no significant change in miRNA expression was obtained between the post-treatment and pre-treatment groups. After treatment, up to two-fold decreases in the expression levels of CCL8, CXCL10, IL17A, IFNG, TNF, IL2RG, TNFRSF1A and IL4 cytokines were detected in the case groups. These results suggest that increased virulence may indicate a delay in early pro-inflammatory response due to the complex activity of host immunity. When all groups were evaluated together, it was revealed that there was no clinically significant relationship between the course of the disease, miRNA and cytokine expressions and bacterial genotypes [36].

Ulger M. et al. [37], in a study comparing plasma levels of miRNA and some cytokines in TB and healthy control groups, detected significant upregulation of miRNAs mir-1, miR-7-5p, miR-10a-5p, miR-9-5p, miR-10b-5p, miR-15b-5p miR-16-5p, miR-25-3p, miR-100-5p, miR-106b-5p, miR-128 -3p, miR-133a-3p, miR-193a-5p, miR-210-3p, miR-143-3p, miR-200b-3p, miR-205-5p, and miR-296-5p in the patient group ($p<0.05$). In addition, IL-10, IL-1β, TNF-α, IFN-γ, and IL-8 levels were significantly higher in the TB group ($p<0.05$). These results indicate a correlation between miRNA and cytokine levels in forming the immune response against bacteria in TB disease. Only IL-4, IL-6, and IL-12/P40 levels were not significantly different ($p>0.05$). For rapid diagnosis of TB infection, combinations of miR-296-5, -5p, miR-10a-5p, miR-15b-5p, miR-10b-5p, miR-100-5p, miR-143-3p, miR-9, miR-200b-3p, miR-193a-5p, miR-210-3p and miR-1 were identified as potential noninvasive markers that consistent with immunological response [37].

In mycobacterial infections, bacteria have developed negative regulators to inhibit the immune response. Bacteria perform this negative regulatory mechanism through miRNAs. Thanks to these mechanisms, they can use macrophages as their main reservoir. They inhibit the production of pro-inflammatory cytokines from turning the immune response of macrophages positive for themselves. This critical balance between macrophages and mycobacteria determines the course of infection [38].

In a study investigating the role of miR-21 in M. bovis BCG and M. tuberculosis infections in mice, it was reported that miR-21 upregulation inhibited the production of proinflammatory cytokines and increased the production of the anti-pro-inflammatory (IL-10 and IL-12) cytokines. This result is cited in the literature as an effective strategy used by miR-21 to escape Mycobacteria's host immune response and establish chronic infection [39].

Numerous studies describe the role of miRNAs in the regulation of inflammatory responses in M. tuberculosis-infected macrophages (Table 1).

Some miRNA species are listed in the literature and play a role in many different steps of the immune system. These miRNAs play a role in many immune events from lipid metabolism to apoptosis, from immune response to macrophage maturation and autophagy, as shown in Table 1.

Conclusion

TB is still one of the deadliest diseases, according to the criteria set by the WHO. Since it is a contagious disease that requires long-term treatment, it continues to be a "global health problem." M. tuberculosis, the causative agent of TB, can maintain its life in macrophages for a long time by disrupting the host's immune system. miRNAs are non-coding nucleotide sequences involved in many vital events and control mechanisms in the cell. It is evident that miRNAs, which have come to the fore with cancer studies, also have important roles in infectious diseases. Pro-inflammatory cytokines are essential in functioning cytokines and many other immune system mechanisms. Depending on the bacterium's ability, the release of pro-inflammatory cytokines from host cells can be stopped, thus increased cytokines increase the likelihood that the bacteria will remain inside the macrophage.

According to the results, determining host mRNA levels in the early inflammation period may be a guide for meeting cytokine levels, preventing disease development, and therapeutic strategies. Studies on this subject are available in the literature. However, developing and conducting in vivo studies, increasing the number of case-control groups, and establishing multicenter research units will prevent early diagnosis and treatment of the global problem of TB.

Scientific Responsibility Statement

The authors accept full scientific responsibility for designing the study, collecting, analyzing, and interpreting data, writing the manuscript, preparing and scientifically reviewing the content, and approving the final version.

Animal and human rights statement

As the study is a review, it does not involve the use of laboratory/ other animals. This review includes studies previously recognized in the literature as having been published according to the statement, "All procedures performed in studies involving human participants conform to the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards". Studies were not conducted by adding human participants again.

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Conflict of interest

The authors declare that there is no conflict of interest.

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